

56. The process of Claim 51 wherein said at least one chondroinductive agent is a combination of dexamethasone and TGF- $\beta$ 1.

57. The method of Claim 51, and further comprising placing said cells in a rigid porous vessel.

58. The method of Claim 57 wherein said rigid porous vessel is a ceramic cube.

59. The process of Claim 51 wherein said glucose is present in said serum-free medium in an amount of from about 3 grams per liter to about 7 grams per liter.

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REMARKS

The claims have been amended in order to place the application in better form.

Claims 14-16, 18-27, 29-35, 37, 38, 40, and 41 have been cancelled without prejudice, and Claims 42-59 have been added. The cancellation of Claims 14-16, 18-27, 29-35, 37, 38, 40, and 41 without prejudice is not to be construed as an admission by Applicants or Applicants' attorneys that such claims are not patentable, and Applicants reserve the right to prosecute such claims in a continuing application.

The cancellation of Claims 22, 33, 40, and 41 obviates the rejection of such claims under 35 U.S.C. 112, second paragraph. The cancellation of such claims, however, is not to be construed as an admission by Applicants or Applicants' attorneys that such claims are unpatentable.

Claims 14, 15, 18, 19, 20, 23, 25, 26, 29, 30, and 34 had stood rejected under 35 U.S.C. 102(b) as being anticipated by Itay, et al. This rejection is respectfully traversed.

The present invention is directed to process for producing chondrocytes, as defined broadly in Claim 42, and to a process for inducing chondrogenesis in mesenchymal stem cells, as defined broadly in Claim 51. Such processes are effected by culturing mesenchymal stem cells in a chemically defined serum-free medium *in vitro* wherein the mesenchymal stem cells are associated in a three-dimensional format. The chemically defined serum-free medium comprises (1) a chemically defined minimum essential medium; (2) ascorbate or an analog thereof; (3) an iron source; (4) insulin or an insulin-like growth factor; (5) at least one chondroinductive agent or factor; and (6) glucose.

Itay discloses implants for repairing defects in cartilage and bone. The implant includes cells expressing a chondrocyte phenotype embedded in a biocompatible matrix having about 20% serum. The cells may be bone marrow progenital cells or mesenchyme originated cells.

Itay, however, does not disclose or even remotely suggest to one of ordinary skill in the art that one can produce chondrocytes from mesenchymal stem cells, or induce chondrogenesis in mesenchymal stem cells by culturing mesenchymal stem cells in a chemically defined serum-free medium as claimed by Applicants. In Itay, the cells are contained in an implant which contains serum. Thus, Itay teaches away from the present invention, and such teaching away from the invention

is indicative of non-anticipation and non-obviousness. (See W.L. Gore & Associates, Inc. v. Garlock, Inc., 220 U.S.P.Q. 303 (C.A.F.C. 1983), at 312; United States v. Adams, 383 U.S. 39 (1966).) Therefore, Itay does not anticipate Applicants' processes as claimed, nor does Itay render Applicants' processes as claimed obvious to one of ordinary skill in the art. It is therefore respectfully requested that the rejection under 35 U.S.C. 102(b) be reconsidered and withdrawn.

Claims 14, 15, 18-20, 23-26, 29-31, 34, and 35 had stood rejected under 35 U.S.C. 102(b) as being anticipated by Bruder, et al. This rejection is respectfully traversed.

Bruder discloses that certain factors, such as compounds within the TGF- $\beta$  super-family, Inhibin A, chondrogenic stimulatory activity factor, bone morphogenic proteins, collagens, and vitamin A analogs, have chondroinductive activity on human mesenchymal stem cells. In Example 3 of Bruder, however, Bruder cultures mesenchymal stem cells in the presence of bioactive factors and serum in order to induce chondrogenic differentiation of the mesenchymal stem cells. Bruder does not disclose or even remotely suggest to one of ordinary skill in the art that one can produce chondrocytes from mesenchymal stem cells or induce chondrogenic differentiation of mesenchymal stem cells by culturing the mesenchymal stem cells in a chemically defined serum-free medium as claimed by Applicants. Bruder, like Itay, also teaches away from Applicants' processes as claimed. Bruder, therefore, does not anticipate Applicants' claimed processes, nor does Bruder render Applicants' claimed processes obvious to one of ordinary skill in the art. It is therefore respectfully requested that the rejection under 35 U.S.C. 102(b) be reconsidered and withdrawn.

Claims 14-16, 18-27, 29-35, 37, 38, 40, and 41 had stood rejected under 35 U.S.C. 103 as being unpatentable over Bruder, at al. in view of Hunziker. This rejection is respectfully traversed.

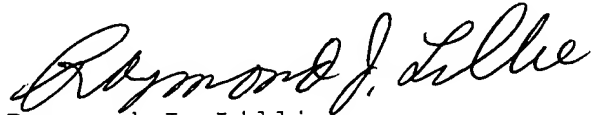
The differences between Applicants' claimed processes and Bruder have been noted hereinabove. Hunziker discloses the treatment and repair of defects or lesions in cartilage by filling the defect or lesion with a biodegradable matrix containing a proliferation agent, a transforming agent, and repair cells. The proliferation agent may be TGF- $\beta$ . The transforming factor, which promotes differentiation of the repair cells into chondrocytes, may be TGF- $\beta$ , TGF- $\alpha$ , FGF, or a combination of TGF- $\beta$  and EGF.

Hunziker, however, does not disclose or even remotely suggest to one of ordinary skill in the art that one can produce chondrocytes from mesenchymal stem cells, or induce chondrogenesis in mesenchymal stem cells by culturing the mesenchymal stem cells in a chemically defined serum-free medium which includes (1) a chemically defined minimum essential medium; (2) ascorbate or an analog thereof; (3) an iron source; (4) insulin or an insulin-like growth factor; (5) at least one chondroinductive agent or factor; and (6) glucose. In addition, Hunziker, when combined with Bruder, which, by virtue of disclosing a serum-containing medium teaches away from Applicants' claimed processes, clearly does not render Applicants' claimed processes obvious to one of ordinary skill in the art.

Applicants and only Applicants have discovered that one can produce chondrocytes from mesenchymal stem cells, or induce chondrogenesis in mesenchymal stem cells by culturing mesenchymal stem cells in a chemically defined serum-free medium including the components hereinabove described. Such processes as claimed by Applicants are not disclosed or even remotely suggested to one of ordinary skill in the art by the cited references. Therefore, for the above reasons and others, the combination of Bruder and Hunziker does not render Applicants' claimed processes obvious to one of ordinary skill in the art, and it is therefore respectfully requested that the rejection under 35 U.S.C. 103 be reconsidered and withdrawn.

For the above reasons and others, this application is in condition for allowance, and it is therefore respectfully requested that the rejections be reconsidered and withdrawn and a favorable action is hereby solicited.

Respectfully submitted,

A handwritten signature in cursive script, reading "Raymond J. Lillie".

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